RE-319 #2

IB03/5877

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***1240/Del/2002*** *dated* ***11th December 2002.***

Witness my hand this 13th day of January 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

1240

A93G 3/00

11 DEC 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR PREPARING A TASTE MASKING COATING COMPOSITION"**

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. RAJESH GANDHI

b. CHAYAPATHY ISSA

c. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

ORIGINAL

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana), INDIA.
Tel. No. (91-124) 6343126; 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, RAJESH GANDHI, CHAYAPATHY ISSA, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representative.

a.

(RAJESH GANDHI)

b. I. Chayapathy

(CHAYAPATHY ISSA)

c. Rajiv Malik

(RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Provisional Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **685792** dated **15.11.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this 9TH day of **DECEMBER, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

1240-D

11 DEC 2002

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

DUPLICATE

A PROCESS FOR PREPARING A TASTE MASKING COATING COMPOSITION

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a taste masking coating composition.

Oral dosage forms are taken by the patient in the form of solutions, emulsions, suspensions, capsules and tablets, the solid forms having the greatest importance because of their good dosability, packaging, transportability, stability and, finally, the ease of intake. Many medicinal substances have an unpleasant or bitter taste, which is why either contact of the medicinal substance with the mucosa of the mouth and pharynx must be prevented or the bitter taste must be masked. If the dosage form is swallowed whole, the unpleasant taste of the medicinal substance is greatly minimized or avoided altogether. However, children, elderly people and many other patients have difficulty in taking tablets and capsules, which have not been broken up. For such patients, pharmaceutically active ingredients are formulated as chewable tablets, mouth-dissolving tablets, dispersible tablets, dry powders for reconstitution or as liquid dosage forms. These dosage forms permit perceptible exposure of the active drug to the taste buds and thus a major requirement of such dosage form is that it must be palatable. Otherwise, the undesirable taste of the formulation creates a feeling of reluctance to taking the medicine.

Coating is a known technique for taste masking of bitter medicaments as it provides a barrier, which prevents the undesirable taste of the medicament from coming through, making the formulation more palatable. Various types of coating can be applied to the drug or dosage form. Taste masking coatings may employ pH dependent or pH independent polymers. Combinations of different polymers are also used to achieve better taste masking. Methacrylic acid polymers alone or in combination with other polymers have been used by various researchers to mask the bitter taste of medicaments. When applied alone, higher amount of polymers are required to mask the bitterness of medicament. Moreover, complete instant release in the entire pH range of GIT (1-8) is not achieved. One of the major drawbacks of the incorporation of methacrylates in higher amount into the formulations is safety and acceptability of formulation. Probably that is why combination of methacrylate with other polymers has been tried.

For example US Pat. No. 6,136,347 describes flavor-masked pharmaceutical compositions comprising microcapsules wherein the said microcapsules comprise a coating of water insoluble neutral methacrylic acid ester copolymers and triethylcitrate.

US Pat. No. 6,106,861 describes a rapidly disintegrable multiparticulate tablet which disintegrates in the mouth in less than 40 seconds and which comprises excipients selected from disintegrating agent, binding agent and an active ingredient in the form of microcrystals coated with a taste masking coating comprising polymethacrylates and cellulose polymers such as hydroxypropyl-methyl cellulose, hydroxypropyl cellulose and cellulose acetophthalates.

PCT application WO 99/44581 describes a process for taste masking of Topiramate by coating the core with coating mixture. The taste masking mixture comprises cellulose acetate, cellulose acetate butyrate, methylcellulose, ethylcellulose or a Eudragit; and a disintegrant.

PCT application WO 98/14179 describes taste-masked microcapsule formulations for water-soluble drugs in a polymeric material consisting essentially of one or more polymers selected from the group consisting of ethyl cellulose, cellulose acetate phthalate, cellulose acetate butyrate, polymethacrylates, hydroxypropyl methyl cellulose phthalate, carboxymethyl ethylcellulose, polylactic acid and combinations thereof.

Thus, a number of taste masking coating compositions are known but none of them is fully satisfactory as complete taste masking combined with rapid release cannot be realized using these compositions. Therefore, there is a need for a taste masking composition, which can provide a dosage form that is both palatable and bioavailable.

In the present invention the above objective has been achieved by using a coating composition, which comprises a combination of (i) copolymers of acrylate and methacrylate with quaternary ammonium group in combination with sodium carboxymethylcellulose and (ii) polyvinyl alcohol-polyethylene glycol copolymer.

Surprisingly, it has been found that when combination of these two polymers are used for coating composition, release rate of the medicament is faster and optimum results were observed with respect to taste masking and release of active components. Moreover, the amount of acrylate and methacrylate copolymers with quaternary ammonium group in combination with sodium carboxymethylcellulose required for coating can also be reduced, thereby, ensuring the safety and acceptability of the dosage form.

Copolymers of acrylate and methacrylate with quaternary ammonium group in combination with sodium carboxymethylcellulose is available under the trade name Eudragit RD 100 supplied by Rohm GmbH, Darmstadt. It provides pH independent fast disintegrating films especially suitable for taste masking purposes. Disintegrant, sodium carboxymethylcellulose is inherently present in the Eudragit RD 100 thereby facilitating fast release of the medicament.

Polyvinyl alcohol-polyethylene glycol copolymer is commercially available under the trade name Kollicoat IR marketed by BASF Corporation. It is highly soluble in water and is used as covering for instantaneous release in tablets.

Therefore, the present invention provides an immediate release taste-masked pharmaceutical composition for oral administration by coating the core containing the bitter or unpleasant tasting drug with a combination of (i) copolymers of acrylate and methacrylate with quaternary ammonium group in combination with sodium carboxymethylcellulose and (ii) polyvinyl alcohol-polyethylene glycol copolymer.

Immediate release according to the present invention is release of the medicament in the gastrointestinal tract within one hour.

The present invention provides a coating that masks the bitter or undesirable taste without delaying the availability of the medicament when consumed orally.

The copolymer of acrylate and methacrylate with quaternary ammonium group in combination with sodium carboxymethylcellulose and polyvinyl alcohol-polyethylene glycol copolymer may be present in a ratio of 1:2 to 1:3.

The concentration of methacrylate-acrylate copolymer may be used at about 20 % w/w to about 30 % w/w and polyvinyl alcohol-polyethylene glycol copolymer from about 65 % w/w to about 75 % w/w of the total taste masking coating composition.

In addition to the above two polymers, the coating composition may also contain lubricants which functions as anti-sticking agent. This may be selected from the group consisting of talc, glyceryl

monostearate, magnesium stearate, colloidal silica and mixtures thereof. The concentration of lubricant may be up to 10% of the dry weight of the taste masking coating composition.

The coating composition of the present invention can be prepared by dispersing polyvinyl alcohol-polyethylene glycol copolymer in purified water under stirring. Then Eudragit is dispersed in the above solution under constant stirring. Talc is added and the stirring is continued for next 20 minutes. The coating suspension is filtered through 250 micron nylon cloth. This coating composition can then be applied for taste masking of bitter medicaments by following any of the procedures such as spray coating, pan coating, fluidized bed coating etc.

The bitter, unpleasant tasting active ingredient can be directly coated with the coating composition or else drug loaded core can be coated with taste masking coating suspension in Fluid Bed Processor to achieve the desired product.

The coating composition of the present invention may be used to mask the taste of any category of bitter drugs. However, active ingredient according to the present invention can be selected from the group consisting of analgesics, antibiotics, gastrointestinal drugs, cardiovascular agents, CNS drugs, antihistamines or cholesterol reducing agents.

Analgesics such as acetaminophen, aspirin, ibuprofen, naproxen, ketoprofen; antibiotics such as cefuroxime axetil, cefpodoxime proxetil, ciprofloxacin, erythromycin, clarithromycin; gastrointestinal drugs such as loperamide, famotidine, ranitidine, cimetidine and salts thereof ; Cardiovascular agents such as ibersartan, captopril, lisinopril and salts thereof ; CNS drugs such as nefazodone, buspirone and salts thereof ; antihistamines such as chlorpheniramine and astemizole; cholesterol reducing agents such as statins can be taste masked using the coating composition of the present invention.

The coated core can be formulated as sprinkles, dry powder, suspension, emulsion, or as whole chewable or dispersible tablet, or any other suitable oral dosage forms.

The coating composition according to the present invention can also be applied to whole dosage form and thus concealing the bitter taste of the medicament.

The following examples illustrate the invention and are not intended to limit the scope of the invention.

Example 1: Dry suspension of Cefpodoxime Proxetil

Drug layering

1. Microcrystalline cellulose beads	190.0mg
2. Cefpodoxime Proxetil (Equivalent to 100mg cefpodoxime)	142.4mg
3. Hydroxypropyl methylcellulose	40.0mg
4. Hydroxy propyl cellulose	20.0mg
5. Crosscarmellose sodium	15.6mg
6. Purified water	qs
7. Isopropyl alcohol	qs

Taste masking layering

1. Drug loaded beads	410.0mg
2. Eudragit RD 100	25.0mg
3. Kollicoat IR	68.5mg
4. Talc	6.5mg
5. Water	qs

Composition of suspension

1. Drug loaded beads	510.0mg
2. Fruit Gum flavor	15.0mg
3. Frescofort flavor	15.0mg
4. Colloidal silicon dioxide	17.5mg
5. Carrageenan	30.0mg
6. Microcrystalline cellulose	10.0mg
7. Sodium citrate	5.0mg
8. Citric acid (Anhydrous)	3.0mg
9. Ferric oxide (Yellow)	0.05mg
10. Sucrose	2994.45mg

Suspension of cefpodoxime proxetil and combination of binders in water (frothing was minimized using small volume of isopropyl alcohol) is sprayed on the microcrystalline cellulose beads (MCC beads) and dried to provide core beads using Fluid Bed Processor. The core beads are then screened to remove fines and agglomerates. The core beads are coated again with a taste masking mixture and then dried in Fluid Bed Processor. Coated beads are sifted to remove fines and agglomerates, prior to encapsulation.

The in-vitro dissolution release of cefpodoxime proxetil from the dry suspension of example 1 was determined in accordance with the procedure cited (Pharmacopoeial Forum, Vol. 23, Number 4, July-Aug. 1997, 4388-4392). Weight equivalent to 5ml suspension was added to 900 ml of Glycine buffer (pH 3.0). Aliquots of 5ml of solution were taken at 15, 30 and 45 minutes, respectively and analyzed spectrophotometrically at wavelength of 259nm.

Table 1: In-vitro dissolution release of dry suspension of example-1

Time (in minutes)	% Drug released
15	62.2
30	85.6
45	95.1

Example 2: Immediate release pellet composition of Cefpodoxime Proxetil

Drug layering

1. Microcrystalline cellulose beads	190.0mg
2. Cefpodoxime Proxetil (Equivalent to 100mg cefpodoxime)	142.4mg
3. Hydroxypropyl methylcellulose	40.0mg
4. Hydroxy propyl cellulose	20.0mg
5. Crosscarmellose sodium	15.6mg
6. Purified water	qs
7 Isopropyl alcohol	qs

Taste masking layering

1. Drug loaded beads	410.0mg
2. Eudragit RD 100	25.0mg
3. Kollicoat IR	68.5mg
4. Talc	6.5mg
5. Water.	qs

Hydroxypropyl methylcellulose, hydroxypropyl cellulose and crosscarmellose sodium are dispersed in purified water under stirring. Then cefpodoxime proxetil is dispersed in the above prepared mixture under constant stirring. Isopropyl alcohol is added and stirring is continued for 30 minutes. Microcrystalline cellulose beads are coated with this cefpodoxime proxetil dispersion in Fluid Bed Processor. Granules are dried till LOD is NMT 4.0 % at 105 °C (on IR Balance). Dried pellets are coated with taste masking coating suspension in Fluid Bed Processor to achieve the desired product.

The in-vitro dissolution release of drug from pellets of example 2 was determined in accordance with the procedure cited (Pharmacopoeial Forum, Vol. 23, Number 4, July-Aug. 1997, 4388-4392). A 0.510 gm sample of coated pellets was added to 900 ml of Glycine buffer (pH 3.0). Aliquots of 5ml of solution were taken at 15, 30 and 45 minutes, respectively and analyzed spectrophotometrically at wavelength of 259 nm.

Table 2: In-vitro dissolution profile of pellet of example-2

Time (in minutes)	% Drug released
15	75.1
30	90.3
45	97.8

WE CLAIM:

1. A process for preparing a taste masking coating composition comprising (i) copolymer of acrylate and methacrylate with quaternary ammonium group in combination with sodium carboxymethylcellulose and (ii) polyvinyl alcohol-polyethylene glycol copolymer.

2. A process for preparing an immediate release taste-masked pharmaceutical composition for oral administration by coating the core containing the bitter, unpleasant tasting drug with a combination of (i) copolymers of acrylate and methacrylate with quaternary ammonium group in combination with sodium carboxymethylcellulose and (ii) polyvinyl alcohol-polyethylene glycol copolymer.

3. The process according to claim 1 or 2 wherein the ratio of the said methacrylate-acrylate copolymer and polyvinyl alcohol-polyethylene glycol copolymer is about 1:2 to 1:3.

4. The process according to claim 1 ~~or 2 wherein the concentration of said methacrylate-acrylate~~ copolymer is about 20 % w/w to about 30 % w/w of the total coating composition.

5. The process according to claim 1 or 2 wherein the concentration of said polyvinyl alcohol-polyethylene glycol copolymer is about 65 % w/w to about 75 % w/w of the total coating composition.

6. The process according to claim 1 or 2 wherein the coating composition comprises lubricant in addition to the said methacrylate-acrylate copolymer and polyvinyl alcohol-polyethylene glycol copolymer.

7. The process according to claim 6 wherein the lubricant is selected from the group consisting of talc, glyceryl monostearate, magnesium stearate, colloidal silica and mixtures thereof.

8. The process according to claim 6 wherein the lubricant is present up to 10% of the dry weight of the coating composition.

9. The process according to claim 2 wherein the coating is about 10-40 % w/w of the core containing drug.

10. The process according to claim 9 wherein the coating is about 25 % w/w of the core containing drug.

11. The process according to claim 2 wherein the drug is selected from the group consisting of analgesics, antibiotics, gastrointestinal drugs, cardiovascular agents, CNS drugs, antihistamines or cholesterol reducing agents.

12. The process according to claim 11 wherein the analgesics are acetaminophen, aspirin, ibuprofen, naproxen, ketoprofen.

13. The process according to claim 11wherein the antibiotics are cefuroxime axetil, cefpodoxime proxetil, ciprofloxacin, erythromycin, clarithromycin.

14. The process according to claim 13 wherein the antibiotic is cefpodoxime proxetil.

15. The process according to claim 11 wherein the gastrointestinal drugs are loperamide, famotidine, ranitidine, cimetidine.

16. The process according to claim 11 wherein the cardiovascular agents are ibersartan, captopril, lisinopril.

17. The process according to claim 11 wherein the CNS drugs are nefazodone, buspirone.

18. The process according to claim 11 wherein the antihistamines are chlorpheniramine and astemizole.

19. The process according to claim 11 wherein the cholesterol reducing agents are statins.

20. The process according to claim 2 wherein taste-masked pharmaceutical composition is formulated as sprinkles, dry powder, suspension, emulsion, or as whole chewable or dispersible tablet, or any other suitable oral dosage forms.

21. The process according to claim 1 wherein taste-masking composition is applied to the drug.

22. A process for preparing a taste-masked pharmaceutical composition by coating the microcrystalline cellulose beads with the drug suspension and further coating the drug loaded beads with a taste masking coating composition comprising (i) 25% w/w of copolymer of acrylate and methacrylate with quaternary ammonium group in combination with sodium carboxymethylcellulose and (ii) 68.5 % w/w of polyvinyl alcohol-polyethylene glycol copolymer of the total taste masking coating composition.

23. A process as described and exemplified herein.

Dated this **10TH** day of **December, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary